REMARKS

Entry of the foregoing, examination and consideration of the above-identified application are respectfully requested. By the present amendment, applicants have canceled claims 5, 9 and 10 and amended claims 3, 4, 6-8 and 11-14. The claims have been amended to change "DNA sequences" to "nucleotide sequences" in order to maintain consistency with newly added claims 15-25 discussed below. Such an amendment finds support at the very least on page 2, lines 9-16.

In addition, the claims have been amended to specify that the claimed nucleotide sequences are random to the extent that they are generated without regard or reference to a wild type sequence. This phrase emphasizes the fact that the random sequences of the present invention contain no bias toward wild type, as was seen in typical mutagenesis experiments known in the art at the time the present invention was made, and that no knowledge regarding the sequence or structure of wild type proteins is required for the claimed methods. This amendment finds support at the very least in the original specification at page 1, lines 14-23, and page 26, line 30 to page 27, line 2 (see the specification of the 06/887,070 application), and is also similarly supported in the present specification at page 8, lines 11-19 and page 28, lines 1-4.

In addition, applicants have added new claims 15-25. These claims, in addition to those filed on March 3, 1999, are submitted for the purpose of initiating an interference between the instant application and U.S. Patents 5,723,323; 5,763,192; 5,817,483;

5,824,514; and 5,814,476 pursuant to 37 CFR §1.607, and, if the Examiner finds it to be appropriate, between Application Serial No. 08/464,327, filed June 5, 1995, Application Serial No. 08/468,468, filed June 5, 1995, and Application Serial No. 08/464,569, filed June 5, 1995, pursuant to 37 CFR §1.604 ("the Kauffman '323 Patent," "the Kauffman '192 Patent," "the Kauffman '483 Patent," "the Kauffman '514 Patent," and "the Kauffman '476 Patent").

Applicant presents the instant amendment in conjunction with a Request for Interference Pursuant to §§ 1.604 and 1.607, wherein exemplary support in the disclosure for each of the newly submitted claims is attached in Appendix B. The information required by 37 C.F.R. §§ 1.604(a) and 1.607(a) is set forth under headings below which correspond to the subsections of §§ 1.604(a) and 1.607(a) to facilitate consideration by the Examiner. Because applicant's effective filing date, July 17, 1986, is earlier than the effective filing date of the patents identified herein (November 20, 1986), the present applicants should be declared the senior party.[1]

Horwitz should be designated the senior party in the interference. The earliest effective filing date of Kauffman for the '192 patents is November 20, 1986, while Horwitz has an effective filing date of July 17, 1986. With respect to the effective filing dates of the other Kauffman patents, and particularly the '483 and '476 patents, MPEP 2308.01 makes it clear that foreign priority under 35 U.S.C. 119 should not be taken into account in determining effective filing dates. Thus, the Kauffman claim for the benefit of the Swiss application should not be taken into account in determining senior party status. Similarly, with regard to the Kauffman '323 and '514 patents, the filing date of the Kauffman PCT application, PCT/CH85/00099, should not be taken into account, but rather the 35 U.S.C. 102(e) date of the PCT application (November 20, 1986) because that is the date that it would be a reference against the Horwitz claims as discussed in MPEP 2308.01.

I. IDENTIFICATION OF THE PATENTS AND APPLICATIONS WHICH INCLUDE SUBJECT MATTER WHICH INTERFERES WITH THE INSTANT APPLICATION

Pursuant to 37 CFR §1.607(a)(1), Applicants request that an interference be declared between the instant application and U.S. Patent Nos. 5,723,323; 5,763,192; 5,817,483; 5,824,514; and 5,814,476 of Kauffman et al.

Pursuant to 37 CFR §1.604(a)(2), the patent applications which are believed to claim subject matter which interferes with subject matter claimed in the present application ("the Kauffman applications") are U.S. Application Serial No. 08/464,327, filed on June 5, 1995, U.S. Application Serial No. 08/468,468, filed on June 5, 1995, and U.S. Application Serial No. 08/464,569, filed on June 5, 1995.

II. PRESENTATION OF PROPOSED COUNT

Attached Appendix A sets forth a proposed Count pursuant to 37 CFR §§ 1.607(a)(2) and 1.604(a)(1). The proposed Count is an alternative Count prepared after consideration of the subject matter claimed by the respective parties.

The proposed Count is at least as broad as the claims of the five Kauffman Patents in that the first half of the proposed Count is identical to all the independent claims of the Kauffman patents. The independent claims of the Kauffman patents include claims 1, 15, 16,

24, 25, 34, 41-45 of the '323 patent, claim 1 of the '192 patent, claims 1-4, 6, 17, 29, 35, and 36 of the '483 patent, claims 1, 11, 12, 18, 27 and 37 of the '514 patent, and claims 1-3, 8, 15, 29, 47, 61, 79, 91 and 103 of the '476 patent.

Because applicants do not have access to the claims of the pending Kauffman applications, applicants were not able to copy these claims. However, it is very likely that the claims of any pending related application should also be included in the interference, given the fact that all the claims in the five issued Kauffman patents are directed to the same patentable invention as disclosed and claimed in the present application. The Examiner is respectfully requested to review any related pending application as to whether such application contains claims which are directed to the same patentable invention as defined by those discussed herein, and determine whether such application or applications should be included in the interference. If necessary, the Examiner is respectfully requested to suggest a claim to applicants corresponding to the claims in any pending application pursuant to 37 CFR 1.605(a) so that all related applications may be included in the interference, and amend the proposed Count.

An alternative Count which includes the Kauffman independent claims and claims identical to the corresponding claims of the instant application is being proposed in part because of the different language utilized by the respective parties to describe the same

patentable invention.[2]

III. IDENTIFICATION OF CLAIMS OF THE KAUFFMAN PATENTS WHICH CORRESPOND TO THE PROPOSED COUNT

Claims 1-48 of the Kauffman '323 Patent define the same patentable invention as claims 1-5 of the Kauffman '192 Patent and as claims 1-53 of the Kauffman '483 Patent and as claims 1-46 of the Kauffman '514 Patent and as claims 1-107 of the Kauffman '476 Patent. These claims correspond to and define the same patentable invention as claims 3, 4, 6-8 and 11-25 of the instant Horwitz application.

All the claims are essentially directed to or based on methods of searching for biologically active nucleotide sequences from among a randomly or stochastically generated population, on the theory that particular novel sequences capable of predetermined or desired biological functions may be identified.[3] The crux of the invention reflected in all the claims rests on the discovery, which was indeed a "leap of faith" at the time the present invention was made, that randomly generated sequences could perform specific biological functions in the

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The phrase "same patentable invention" is used herein in the context of 37 CFR §1.601(n) to indicate that the inventions are the same or obvious in view of each other and should therefore be involved in an interference. The phrase should not be taken as an admission that any particular Kauffman claim is patentable under 35 U.S.C. §§ 102, 103 or 112.

Although it is not clear what the term "stochastic" means, applicants assume it has the same meaning as "random" as used in the present application.

absence of millions of years of evolutionary refinement. While many of the claims in the various Kauffman patents incorporate additional steps beyond the generation and screening of or selecting for randomly generated sequences having a particular function, such steps do not make a patentable difference when considering the state of the art at the time.

Indeed, as will be discussed herein, it was known at the time that polynucleotides could be cloned into expression vectors, and that such vectors could be transformed into and amplified in an appropriate host cell. It was known that such a host cell could be analyzed, tested or selected based on whether it expressed the protein encoded by or displayed the function provided by the cloned nucleotide sequence. It was known that vector could then be isolated from identified transformed cells and the cloned nucleotide sequence could then be isolated from the vector using standard techniques in the art, i.e., restriction and gel purification. And it was known that such host cells could be used to produce the recombinant protein, which could be purified and used for whatever purpose it was sought, i.e., for vaccine development, as a drug, to raise antibodies, etc. Such manipulations of nucleic acids and standard recombinant techniques do not impart a patentable distinction to the novel premise at the time that a completely random population of nucleotides could generate a sequence having a particular biological activity.

Likewise, while many of the claims in the various Kauffman patents incorporate limitations which more precisely define the manner in which nucleotide sequences are generated, or the manner in which nucleotide sequences are screened, or the particular

predetermined or desired property of the nucleotide sequence identified, these specific limitations are merely variations of the general concept, and apparent applications of the method, given the state of the art at the time.

Indeed, it was known that nucleotide sequences could be synthesized chemically or by using enzymes like polymerase and terminal transferase. It was known that new nucleotide sequences could be generated by ligating smaller nucleotide sequences together. It was known that DNA could be cleaved with restriction enzymes and re-ligated using DNA ligase following hybridization of the "sticky ends" of the cleaved DNA. And it was also known that DNA could be ligated in the absence of complementary ends, i.e., blunt-end ligation.

Thus, while there are many claims which have issued in the five Kauffman patents, each merely rephrases the crux of the invention, or adds or specifies particular steps, which would have been apparent to a person skilled in the art when the basic novelty of the invention is taken in view of the state of the art. Therefore, all the claims of each Kauffman patent are believed to correspond to the Count pursuant to 37 CFR §1.607(a)(3) for the following reasons, with each patent discussed separately for the Examiner's convenience.

The Kauffman '323 Patent

The proposed Count includes Kauffman '323 claims 1, 15, 16, 24, 25, 34, 41-45 joined individually by "or" to each other and independent claims from the other four Kauffman patents. Kauffman '323 claims 1, 15, 16, 24, 25, 34, 41-45 thus each correspond exactly to

one part of the proposed Count. Because of the use of "or," correspondence to one part of the proposed Count is sufficient.

'323 claims 1-14

Thus, '323 claim 1 corresponds to the Count because it is included as an alternative part of the Count. However, it is noted that '323 claim 1 would also correspond to the Count in that it is obvious in view of '192 claim 1, which also corresponds exactly to the Count. '323 claim 1 differs from '192 claim 1 in that it defines the predetermined property of the peptide, polypeptide or protein as a "binding property to a ligand." However, such a property would have been an apparent application of the method recited in '192 claim 1, because it was known in the art at the time that cloned nucleotide sequences could be used to produce peptides, which could be identified by virtue of a binding property. *See*, *i.e.*, Matteucci and Heyneker (1983) (attached), describing antibody screening of recombinant proteins; *see also*, the present application at page 7, lines 26-29, discussing enzyme and enzyme-substrate reactions as a method to screen for the presence of peptide.

Nevertheless, '323 claim 1 corresponds exactly to part of the Count. Claims 2-14 of the '323 patent all depend from '323 claim 1 and define the same patentable invention as '323 claim 1. '323 claims 2-14 therefore also correspond to the Count. For instance, claim 14 specifies that step (c) of claim 1 further comprises digesting the stochastic population of expression vectors with a restriction enzyme and religating the pieces to generate new

stochastic sequences. Such a step would have been an obvious extension of the method of '323 claim 1, because the fact that new sequences could be generated by ligating together restriction fragments was well-known in the art at the time the Kauffman application was filed. *See, i.e.,* Shortle (1983), p. 184, describing the generation of new mutant genes by digesting with restriction enzymes and inserting restriction fragments.

'323 claims 15 and 42

Kauffman '323 claim 15 corresponds to the Count because it is included in the Count as discussed above. However, it is noted that '323 claim 15 is directed to an isolated, diverse population of peptides, polypeptides or proteins comprising greater than about 1 X 10^5 different stochastic amino acid sequences encoded by stochastic polynucleotide sequences. This claim is obvious in view of, at the very least '323 claim 1, which is directed to a method of identifying a peptide, polypeptide or protein from a diverse population of peptides, polypeptides or proteins expressed by host cells containing stochastically generated polynucleotide sequences. Once one has produced a population of peptides or proteins using recombinant DNA technology, one could have readily separated the peptides or proteins from the host cells to create an isolated population of diverse peptides, polypeptides or proteins using standard techniques known in the art, i.e., see Kauffman '323 col. 10, lines 13-31, discussing how purification of particular proteins and populations of proteins can be "carried out by established procedures." Hence, although '323 claim 15 corresponds to the Count

because it is part of the count, it also corresponds because it is obvious over '323 claim 1 in view of the state of the art at the time.

Similarly, '323 claim 42 corresponds to the Count because it is included as part of the Count. However, '323 claim 42 is also directed to an isolated, diverse population of peptides encoded by stochastic polynucleotide sequences (as is '323 claim 15), but specifies that the polynucleotide sequences are 300 nucleotides or less. Since limiting the length of the stochastic polynucleotide sequences would not present a patentable distinction, '323 claim 42 would also correspond to the Count in the same manner that claim 15 corresponds to the Count, since it is obvious in view of claim 1.

'323 claims 16-24 and 43

Kauffman '323 claim 16 corresponds exactly to part of the Count. Claims 17-23 all depend from '323 claim 16 and define the same patentable invention as '323 claim 16. '323 claims 17-23 therefore also correspond to the Count. While '323 claim 24 exactly corresponds to part of the Count, it is noted that '323 claim 24 is directed to an isolated, diverse population of polynucleotide sequences and would be obvious in view of claim 16, which recites a method of isolating a polynucleotide sequence following screening of host cells expressing stochastically generated polynucleotide sequences. If one could isolate a particular polynucleotide sequence from among a diverse, stochastic population, then isolating the population itself would be a clear variation, since methods for isolating a population of vectors

were known at the time the Kauffman was made. *See, i.e.,* Maniatis et al. Molecular Cloning: A Laboratory Manual, Cold Spring Harbor, New York (1982), p. 2 (attached). '323 claim 24 therefore also corresponds to the Count, to the extent that it is obvious in view of claim 16 when viewed with the state of art at the time.

'323 claim 43 corresponds to the Count in the same manner that claim 24 corresponds to the Count. While claim 43 is included as part of the Count, since claim 43 is also directed to an isolated, diverse population of polynucleotide sequences which is only further defined by limiting the stochastically generated polynucleotide sequences to 300 or bases or less. Since limiting the length of the stochastic sequence does not impart a patentable distinction, claim 43 would also be obvious in view of claim 16, and therefore also corresponds to the Count as an apparent variation of claim 16.

'323 claims 25-33

Kauffman '323 claim 25 corresponds exactly to part of the Count. Claims 26-33 all depend from '323 claim 25 and define the same patentable invention as '323 claim 25. '323 claims 26-33 therefore also correspond to the Count. For instance, '323 claim 30 specifies that the stochastically generated polynucleotide sequences of claim 25 are generated by "stochastic copolymerization." While the '323 specification does not make it clear what "stochastic polymerization" means, claims 95 and 96 of the '476 patent indicate that such "copolymerization can be accomplished by either hybridization of complementay sequences or

by ligation. Ligation was certainly a well known technique for joining together segments of nucleic acids at the time the Kauffman application was filed. Hence, specifying that the stochastic polynucleotide sequences were generated by "stochastic copolymerization" does not provide a patentable distinction in view of the state of the art at the time. Thus, claim 30 would also correspond to the Count, because it is directed to the same patentable invention as claim 25.

Likewise, claim 33 specifies that step (c) of the method of claim 25 further comprises digesting the vectors with a restriction enzyme and religating the pieces to form a new different population. Ligating together restriction fragments to form new sequences was well known in the art at the time the Kauffman application was filed. *See*, Shortle (1983) (attached). Thus, claim 33 does not provide a patentable distinction over claim 25 when taken in view of the art, and would therefore also correspond to the Count.

'323 claims 34-41 and 44

'323 claim 34 corresponds exactly to part of the Count. Claims 35-40 all depend from '323 claim 34 and define the same patentable invention as '323 claim 34. '323 claims 35-40 therefore also correspond to the Count, in much the same manner as claims 26-33 correspond to the Count because they are dependent on claim 25.

'323 claim 41 is directed to an isolated, diverse population of vectors comprising stochastically generated polynucleotide sequences, and is obvious in view of, at the very least

claim 34, which recites a method of producing stochastically generated polynucleotide sequences by inserting them into a population of vectors. While claim 41 corresponds to the Count because it is part of the Count, since techniques for cloning DNA sequences into vectors and methods for isolating vectors were well known techniques at the time the Kauffman application was filed, i.e., *see* Maniatis (1982), claim 41 is also obvious in view of claim 34, and therefore corresponds to the Count also because claim 34 is part of the Count.

'323 claim 44 would correspond to the Count in the same manner that claim 41 corresponds to the Count, since claim 44 is also directed to an isolated, diverse population of vectors which is only further defined by limiting the stochastically generated polynucleotide sequences to 300 or bases or less. So, although claim 44 corresponds to the Count because it is part of the Count, since limiting the length of the stochastic sequence does not impart a patentable distinction, claim 44 would also be obvious in view of claim 34, and therefore also corresponds to the Count in this manner.

Finally, claims 45-48 are product-by-process claims directed to an isolated, diverse population of peptides, polypeptides or proteins comprising stochastic amino acid sequences where the peptides are expressed from stochastically generated polynucleotide sequences, and the stochastically generated polynucleotide sequences used to express the population of peptides are generated by copolymerization of oligonucleotides or chemical synthesis. Since both the processes of joining or ligating together oligonucleotides and chemically synthesizing oligonucleotides were well known in the art at the time the Kauffman application was filed,

i.e., *see* Maniatis, (1982) pp. 11-14 (attached), claims 45-48 would have been apparent to those of ordinary skill in the art in view of the method already set forth in '323 claim 1, which recites a method of identifying a peptide, polypeptide or protein from a stochastic population of peptides or proteins expressed from a population of stochastic polynucleotide sequences. Thus, claims 45-48 are an apparent extension of '323 claim 1, and would correspond to the Count since '323 claim 1 is part of the Count, even though they also correspond to the Count because they are part of the Count.

Thus, all of the claims of the Kauffman '323 patent correspond to the proposed Count, because they are included as an alternative, are dependent on those included, or are obvious over those included as part of the Count.

The Kauffman '192 Patent

'192 claims 1-5

The proposed Count includes Kauffman '192 claim 1 joined by "or" to independent claims from the other four Kauffman patents. Kauffman '192 claim 1 thus corresponds exactly to one part of the proposed Count. Because of the use of "or," correspondence to one part of the proposed Count is sufficient.

Kauffman '192 claims 2-5 are dependent on '192 claim 1 and therefore define the same patentable invention. '192 claims 2-5 therefore also correspond to the Count. In particular,

claims 2 and 3 specify that the predetermined property of the peptide, polypeptide or protein produced by the method of '192 claim 1 has a "binding property" defined as an antigenic epitope, which may be identified by specific antibodies, respectively. Since screening by virtue of antibody reactivity was a well known technique at the time the Kauffman application was filed, i.e., *see* Matteucci and Heyneker (1983), describing a radioimmune assay (RIA) of transformed cells expressing recombinant protein, a peptide or protein having such a "binding property" would be an obvious extension of the method of '192 claim 1 given the state of the art at the time.

Likewise, '192 claims 4 and 5 further specify that the proteins identified using the antibody are used to make a vaccine, and more specifically, an anti-hepatitis vaccine. Using peptides and proteins to vaccinate animals against subsequent infection by the native foreign agent were well known in the art at the time the Kauffman application was filed, i.e., *see* McAleer et al. (1984), which describes a hepatitis vaccine made from recombinantly produced viral protein; and Kleid et al. (1981), which describes the use of recombinantly produced foot-and-mouth disease viral protein as a vaccine (both attached). Therefore, claims 4 and 5 are obvious over the method recited in '192 claim 1 in view of the state of art at the time, and would therefore also correspond to the Count.

The Kauffman '483 Patent

The proposed Count includes Kauffman '483 claims 1-4, 6, 17, 29, 35, and 36 joined

by "or" to independent claims from the other four Kauffman patents. Kauffman '483 claims 1-4, 6, 17, 29, 35, and 36 thus each correspond exactly to one part of the proposed Count. Because of the use of "or," correspondence to one part of the proposed Count is sufficient.

'483 claims 1 and 2

While '483 claim 1 exactly corresponds to one part of the Count, it would also correspond to the Count because it is obvious in view of '192 claim 1 when taken in view of the state of the art at the time the first Kauffman application was filed. '483 claim 1 is directed to a process for the production of a peptide, polypeptide or protein identified by screening or selecting host cells carrying a library of expression vectors containing stochastically generated polynucleotide sequences, whereby the polynucleotide sequences are generated by "synthetic polynucleotide coupling." While the meaning of the phrase "stochastic polynucleotide coupling" is not clear in view of the '483 specification, it may refer to a method whereby stochastic sequences are produced by ligating stochastic oligonucleotides together to form a larger polymer. Since it was known in the art that oligonucleotides both with and without cohesive ends could be ligated together, i.e., *see* Maniatis, (1982) pp. 8-9, and Lewin, Genes II, John Wiley & Sons, N.Y. (1983), p. 285 (attached), building stochastic sequences in this manner would merely be an apparent variation of the main concept of generating stochastic sequences, to be screened for a predetermined property. Thus, while '483 claim 1 corresponds exactly to part of the Count, it also corresponds to the Count because it is an apparent variation

by "or" to independent claims from the other four Kauffman patents. Kauffman '483 claims 1-4, 6, 17, 29, 35, and 36 thus each correspond exactly to one part of the proposed Count. Because of the use of "or," correspondence to one part of the proposed Count is sufficient.

'483 claims 1 and 2

While '483 claim 1 exactly corresponds to one part of the Count, it would also correspond to the Count because it is obvious in view of '192 claim 1 when taken in view of the state of the art at the time the first Kauffman application was filed. '483 claim 1 is directed to a process for the production of a peptide, polypeptide or protein identified by screening or selecting host cells carrying a library of expression vectors containing stochastically generated polynucleotide sequences, whereby the polynucleotide sequences are generated by "synthetic polynucleotide coupling." While the meaning of the phrase "stochastic polynucleotide coupling" is not clear in view of the '483 specification, it may refer to a method whereby stochastic sequences are produced by ligating stochastic oligonucleotides together to form a larger polymer. Since it was known in the art that oligonucleotides both with and without cohesive ends could be ligated together, i.e., *see* Maniatis, (1981) pp. 8-9, and Lewin, Genes II, John Wiley & Sons, N.Y. (1983), p. 285 (attached), building stochastic sequences in this manner would merely be an apparent variation of the main concept of generating stochastic sequences, to be screened for a predetermined property. Thus, while '483 claim 1 corresponds exactly to part of the Count, it also corresponds to the Count because it is an apparent variation

of the method recited in claim 1 of Kauffman '192.

'483 claim 2 also corresponds exactly to part of the Count. Yet, '483 claim 2 would also correspond to the Count in view of, at the very least, '192 claim 1, since the only substantive difference between the claims is that '483 claim 2 specifies that the polynucleotides produced are "at least partially" stochastic. Since "completely" is a species of "at least partially," clearly one could generate "at least partially" stochastic sequences if one knew how to generate completely stochastic sequences. Indeed, one generates "partially" stochastic nucleotide sequences when cloning a population of completely stochastic nucleotide sequences into an expression vector. Thus, '483 claim 2 would be obvious over '192 claim 1 and '483 claim 1, and therefore corresponds to the Count as an apparent variation as well as an exact part of the Count.

'483 claims 3-5

'483 claims 3 and 4 are directed to methods of detecting a ligand by screening a population of peptides, polypeptides or proteins produced by stochastically generated polynucleotide sequences. Claim 3 merely differentiates over claim 4 by specifying that the stochastic polynucleotides are produced by synthetic coupling, which was a well known way to synthesize a polynucleotide sequence at the time the Kauffman application was filed as discussed above. Thus, '483 claims 3 and 4 are each merely an alternative way of looking at a method of screening a population of peptides for the ability to bind to a ligand. Thus, '483

claims 3 and 4 are apparent variations of, at the very least '192 claim 2, and would therefore correspond to the Count in an obvious manner, even though each exactly corresponds to part of the Count. In addition, since '483 claim 5 is dependent on either claim 3 or 4, it is directed to the same patentable invention and also corresponds to the Count.

'483 claims 6-16

'483 claim 6 exactly corresponds to part of the Count. '483 claims 7-16 either directly or indirectly depend from claim 6, and therefore define the same patentable invention. Thus, claims 7-16 also correspond to the Count. For instance, translating polynucleotide sequences to produce polypeptides (as recited in '483 claims 7 and 10) was certainly known in the art. Indeed, the basic premise of recombinant DNA technology was to express nucleic acid sequences, i.e., transcribe and translate, to produce recombinantly derived proteins. Synthesizing "at least partially" stochastic sequences as recited in claims 8 and 11 would be an obvious extension of the synthesis of completely stochastic sequences as discussed above. Of course, it was also known that sequences could be cloned and "amplified" in vivo (as encompassed by '483 claim 9) by virtue of high copy number cloning vectors at the time the first Kauffman application was filed, i.e., *see* Muller et al. (1978), p. 345 (attached). Likewise, isolating a cloned polynucleotide sequence by isolating a plasmid was also known, i.e, *see* id.(attached). Again, screening by binding or chemical catalysis, as recited in '483 claims 13, 15 and 16, was a well known way to screen a library at the time, as was improving

a predetermined property by mutagenesis as recited in '483 claim 14 (see the instant specification at page 8, lines 4-5, discussing McClure (1985) Ann. Rev. Biochem. 54: 171-204).

'483 claims 17-28

'483 claim 17 corresponds exactly to part of the Count. Claims 18-28 are dependent on claim 17 in much the same manner as claims 7-16 are dependent on claim 6, which was discussed at length above. Thus, claims 18-28 also correspond to the Count in that they define the same patentable invention as '483 claim 17.

For instance, claim 24 is dependent on claim 17 and specifies that step (d) of claim 17, "producing said peptide or protein," comprises "chemical synthesis or recombinant expression." Thus, claim 24 merely states that the protein may be produced recombinantly using the polynucleotide identified in step (c), or may be synthesized chemically, presumedly based on knowledge gleaned from the nucleotide sequence of the isolated polynucleotide. However, the use of genetic information to express proteins, and chemical synthesis of peptides based on genetic information, were both known in the art the time the Kauffman application was filed. *See, i.e.*, "The Science Used in the Recombinant DNA Industry," Chapter 18 from Watson, Tooze and Kurtz (1983) (attached). Thus, it would have been clear to those of skill in the art when faced with claim 17 of the '483 patent that the peptide, polypeptide or protein could be produced recombinantly or synthetically. Claim 24 therefore corresponds to the Count,

because it is directed to the same patentable invention as claim 17 of the '483 patent.

'483 claims 29-34

'483 claim 29 corresponds exactly to part of the Count. Claims 30-34 are dependent on claim 29 and merely specify various known ways to synthesize polynucleotide sequences. Thus, claims 30-34 define the same patentable invention as '483 claim 29, and are obvious in view of claim 29 and the state of the art at the time the Kauffman application was filed. Thus, '483 claims 30-34 also correspond to the Count.

'483 claims 35-38

'483 claims 35 and 36 correspond exactly to individual parts of the Count. In addition, it is noted that claims 35 and 36 merely recite in alternative ways known uses of a peptide or protein to catalyze a reaction between two or more reactant precursors. Given that the method of the invention permits the identification or isolation of specific peptide or protein sequences from a stochastic population by any means, including by virtue of their capability to catalyze a chemical reaction, claims 35 and 36 merely recite what would have been a standard use of a stochastic population of peptides or proteins given the state of the art. Thus, '483 claims 35 and 36 correspond to the Count not only because they are individually included in the Count, but also because they would have been obvious over the other claims, i.e., '483 claims 6 or 17 at the least.

Claims 37 and 38 are dependent on claim 36 of the '483 patent and merely specify that the steps are repeated on a smaller population taken from the entire population of stochastic peptides, polypeptides or proteins. Thus, claims 37 and 38 define the same patentable invention, and also correspond to the Count.

'483 claims 39-53

Claims 39-53 are dependent on either claim 6, claim 17 or claim 29, each of which corresponds exactly to part of the Count. In fact, claims 39-53 merely specify various sizes of populations of amino acid and polynucleotide sequences which may be employed in the methods recited in the independent claims. Since size of the stochastic library would not constitute a patentable distinction over the general method, claims 39-53 also correspond to the Count.

Thus, all of the claims in the Kauffman '483 patent correspond to the proposed Count.

The Kauffman '514 Patent

The proposed Count includes Kauffman '514 claims 1, 11, 12, 18, 27 and 37 joined by "or" to independent claims from the other four Kauffman patents. Kauffman '514 claims 1, 11, 12, 18, 27 and 37 thus each correspond exactly to one part of the proposed Count. Because of the use of "or," correspondence to one part of the proposed Count is sufficient.

'514 claims 1-10

'514 claims 2-10 are dependent on '514 claim 1. Thus, claims 2-10 define the same patentable invention as claim 1, and would also correspond to the Count. For instance, claims 3 and 7 add that the process for producing an expression vector comprising a stochastic sequence of polynucleotides as recited in '514 claim 1 includes a further step whereby the vector is cut with a restriction enzyme and religated. As discussed above, generating new sequences by ligating together restriction fragments was known at the time the Kauffman application was filed. *See, i.e.,* Shortle (1983). Thus, claims 3 and 7 do not patentably distinguish over '514 claim 1.

'514 claims 11-12

'514 claim 11 corresponds exactly to part of the Count. Nevertheless, claim 11 would also be obvious in view of various other claims which also correspond exactly to the Count in that it merely recites a method which involves a specific way of synthesizing stochastic polynucleotide sequences. Specifically, the method requires addition of polynucleotides to the 3' end of a linearized vector with terminal transferase in order to synthesize a stochastic sequence, and a filling in of the second strand with a polymerase enzyme, both of which were known in the art at the time the Kauffman application was filed, and would have been apparent ways to synthesize a stochastic population of polynuclectides given the concept and motivation to do so. *See, i.e.,* Damiani et al. (1982) (attached).

'514 claim 12 corresponds exactly to part of the Count. '514 claims 13-17 are dependent on claim 12, and some are alternatively dependent on claim 1 or 11. Yet none of claims 13-17 provides a patentable distinction over the independent claims on which they depend. In fact, claims 13, 14 and 17 are product-by-process claims, and claim 15 merely specifies that the translation product is selected from the group consisting of a peptide, polypeptide or a protein. Claim 16 indicates that the transcription product can be RNA or DNA. Given the fact that reverse transcription of RNA to generate a cDNA was known in the art at the time the Kauffman application was filed, i.e., see Rhode et al. (1981), it would have been clear to one of skill in the art that the claimed method could be applied just as easily to a stochastic population of RNA as well as DNA. Thus, claims 13-17 do not patentably distinguish over the claims on which they depend. Since the Kauffman independent claims all correspond exactly to part of the Count, '514 claims 13-17 also correspond to the Count.

'514 claims 18-26

'514 claim 18 also corresponds exactly to part of the Count. Even so, it is noted that claim 18 is similar to claim 12 in that it is directed to a method of producing a library or population of vectors, but claim 18 specifies that the size of the library is greater than about 1 X 10^5, and that the library may be synthesized by stochastic polymerization of double stranded oligonucleotides or nucleotide triphosphates presumedly directly on the vector, whereas claim 12 specifies that the stochastic sequences are first synthesized, then ligated into the vector.

Since neither the size of the library nor the manner of synthesizing the stochastic sequences provides a patentable distinction over the general concept and motivation for doing so, claim 18 would also correspond to the Count because it is an apparent variation of claim 12. Likewise, since claims 19-26 are dependent on claim 18, they would also correspond to the Count since they define the same patentable invention as '514 claim 18, in much the same manner as several other sets of Kauffman dependent claims discussed at length above.

'514 claims 27-36

'514 claim 27 also corresponds exactly to part of the Count. However, claim 27 is also obvious over either claim 12 or claim 18 of the '514 patent since it recites a method of copolymerizing vectors containing double-stranded polynucleotides, and vectors are actually a form of polynucleotides. Hence, claim 27 corresponds to the Count also because it is obvious over claims 12 and 18 of the '514 patent. Furthermore, since claims 28-36 are dependent on claim 27 and therefore define the same patentable invention, '514 claims 28-36 also correspond to the Count.

'514 claims 37-46

'514 claim 37 corresponds exactly to part of the Count. However, '514 claim 37 is merely an extension of claim 18 in that it recites a method of stochastically copolymerizing double-stranded polynucleotides onto vectors which already contain stochastic or diverse

polynucleotide sequences. Adding further stochastic sequences to vectors which already contain such sequences to begin with is really no different than a method of adding stochastic sequences to a vector as recited in claim 18. Thus, '514 claim 37 also corresponds to the Count in that it would have been obvious in view of claim 18. Claims 38-46 of the '514 patent are dependent on claim 37, and would therefore correspond to the Count because they define the same patentable invention as '514 claim 37.

Thus, all the claims in the Kauffman '514 patent correspond to the proposed Count.

The Kauffman '476 Patent

The proposed Count includes Kauffman '476 claims 1-3, 8, 14, 15, 29, 47, 61, 79, 91 and 103 joined by "or" to independent claims from the other four Kauffman patents. Kauffman '476 claims 1-3, 8, 14, 15, 29, 47, 61, 79, 91 and 103 thus each correspond exactly to one part of the proposed Count. Because of the use of "or," correspondence to one part of the proposed Count is sufficient.

'476 claims 1, 2 and 8

Although '476 claim 1 corresponds exactly to part of the Count, '476 claim 1 would also correspond to the Count in view of '514 claim 12, since the only substantive difference between these claims is that '476 claim 1 adds a step of using the isolated vector or

polynucleotide sequence to produce a transcription or translation product having the predetermined property. The fact that nucleic acids could be used to transcribe or translate desired products was well known in the art at the time the Kauffman application was filed. Thus, '476 claim 1 would have been an apparent extension of '514 claim 12, therefore '476 claim 1 would correspond to the Count in this manner as well.

Likewise, '476 claim 2 corresponds exactly to part of the Count. However, '476 claim 2 is almost a precise duplicate of '476 claim 1, and would also correspond to the Count in an obvious manner in view of '514 claim 12. The only difference between '476 claims 1 and 2 is that claim 2 specifies that a "population" of stochastic polynucleotides is produced and inserted into a vector (rather than a single stochastic polynucleotide sequence as recited in '476 claim 1). Although the meaning of "stochastic" is not exactly clear in view of the '476 specification, it appears to have no meaning in the context of a single polynucleotide sequence, since some amount of diversity is apparently required. *See, i.e.,* Kauffman '323, claim 24. If one isolates a "stochastic" polynucleotide sequence, by implication, one isolates a stochastic population. Therefore, '476 claim 2 is obvious over '476 claim 1 and '514 claim 12, and would correspond to the Count in this manner as well.

Similarly, '476 claim 8 corresponds exactly to part of the Count. However, '476 claim 8 is obvious in view of '476 claim 1, since a method of producing an RNA is merely a subset of a method of producing a transcription product as claimed (as discussed above for '514 claim 16). Hence, '476 claim 8 also corresponds to the Count because it is obvious in view of '476

claim 1. Since '476 claims 9-14 are dependent on either claim 1, 2 or 8, these claims would also correspond to the Count since they define the same patentable invention.

'476 claims 3-7

'476 claim 3 corresponds exactly to part of the Count. Because '476 claims 4-7 are dependent on claim 3, they would also correspond to the Count because they define the same patentable invention. In particular, claims 4-7 specify that the polynucleotide produced by the method of claim 3 has a capacity to bind to a compound, which is more specifically defined as a protein, and even more specifically defined as a protein which controls the transcription or replication of DNA. It was known in the art at the time the Kauffman application was filed that some genes contain an "enhancer" region which regulates transcription from the promoter. For instance, see the attached abstracts of Weiner and Botchan (1984); Zaret and Yamamoto (1984); Jost et al. (1984); and Pavvar et al. (1983), each of which describes proteins which bind to upstream enhancer elements. Similarly, see the chapter entitled "The Genetic Elements That Control Gene Expression" from Watson, Tooze and Kurtz (1983), where the action of inducers and repressors of gene expression is illustrated by reference to the lactose operon of *E. coli*. Thus, dependent claims 4-7 are obvious in view of independent claim 3 when viewed against the state of the art at the time, and would also correspond to the Count.

'476 claims 15-28

Likewise, '476 claim 15 corresponds exactly to part of the Count. Because '476 claims 16-28 are dependent on claim 15, they would also correspond to the Count since they define the same patentable invention. For instance, claim 17 further specifies that the population of stochastic polynucleotide sequences is amplified. It was common knowledge in the art at the time the Kauffman application was filed that cloned DNA could be amplified in vivo using certain plasmid vectors. *See, i.e.,* Muller et al. (1978), p. 345, which describes chloramphenicol-induced amplification of cloned DNA in a plasmid, and Maniatis, (1982) p.3.

Claims 19 and 20 are also dependent on claim 15 and specify that the claimed polynucleotides can be either RNA or DNA. It was known in the art at the time the Kauffman application was filed that RNA's could have "predetermined properties" other than the translation of proteins. For instance, see Pace and Marsh (1985) which reviews types of catalytic RNA known at the time, and Guerrier-Takada et al. (1983), which describes the catalytic activity of the RNA moiety of *E. coli* ribonuclease P in cleaving tRNA precursors. *See also*, Rhode et al. (1981), disclosing the synthesis of cDNA from RNA using reverse transcriptase. Thus, it would have been apparent to those of ordinary skill in the art when presented with '476 claim 15 that "polynucleotide" could also refer to RNA in a variety of contexts, given the many biological functions of RNA. Thus, claims 19 and 20 would correspond to the Count because they provide no patentable distinction over claim 15, on which they are dependent, and claim 15 exactly corresponds to part of the Count.

Also, claim 23, as another example, is indirectly dependent on claim 15 and specifies that the claimed method further comprises improving the predetermined property of the polynucleotide by in vitro or in vivo mutagenesis. This also would have been a well known extension of the method recited in claim 15, as discussed previously and reviewed in the present specification at page 35, lines 2-3 and page 8, lines 4-5.

'476 claims 47-60

Although claim 47 of the '476 patent corresponds exactly to part of the Count, it is noted that claim 47 would also correspond to the Count because it is obvious over '476 claim 15. The only distinction between these two claims is that '476 claim 47 adds a step of isolating the polynucleotide sequence identified as having a predetermined property. Since methods of isolating polynucleotides were well known in the art at the time the Kauffman application was filed, claim 47 of the '476 patent would have been a clear extension of claim 15. Additionally, since claims 48-60 are dependent on claim 47 in the same manner that claims 16-28 are dependent on claim 15, they would also correspond to the Count since they define the same patentable invention.

'476 claims 29-46

Similarly, claim 29 corresponds exactly to part of the Count. However, '476 claim 29 is also obvious in view of claim 15, since the only distinction is that it specifies that the

predetermined property of the polynucleotide is the ability to bind a ligand. Proteins that bind to polynucleotide sequences were well known in the art at the time the Kauffman application was filed as discussed above, i.e., *see* Pavvar et al., which shows that transcriptional regulatory proteins which bind to DNA were known at the latest in 1983. Furthermore, the strategy of screening a DNA library by virtue of a binding activity was also known as discussed above and evidenced by Matteucci and Heyneker (1983). Thus, claim 29 would also be obvious in view of claim 15, and also corresponds to the Count in this manner.

Additionally, because claims 30-46 are dependent on '476 claim 29, they would also correspond to the Count because they define the same patentable invention. In particular, '476 claim 41 adds a further step whereby the population of vectors is digested with a restriction enzyme such that the cloned stochastic sequences are digested, then reinserted to create new sequences. Such techniques for reassembling or creating new DNA sequences were known in the art at the time the Kauffman application was filed as discussed above, i.e., *see* Shortle (1983). Thus, the additional step recited in claim 41 would have been an obvious extension of the method recited in claim 29, and claim 41 would also correspond to the Count as being obvious in view of the state of the art.

<u>'476 claims 61-78</u>

'476 claim 61 is obvious in view of claim 29 in the same manner that claim 47 is obvious over 15. The only distinction between these two claims is that '476 claim 61 adds a

step of isolating the polynucleotide sequence identified as having a predetermined property. Since methods of isolating polynucleotides were well known in the art at the time the Kauffman application was filed, claim 61 of the '476 patent would have been an obvious extension of claim 29. Additionally, since claims 62-78 are dependent on claim 61, they would also correspond to the Count since they define the same patentable invention. In particular, claim 73 adds a restriction/ re-ligation step as discussed above for claim 41, and would be obvious over claims 61 and 29 in view of the state of the art at the time, i.e., see Shortle (1983).

'476 claims 79-90 and 103-107

'476 claim 79 corresponds exactly to part of the Count. Nevertheless, it would also correspond to the Count in that it is obvious over any one of a number of claims in all five of the Kauffman patents. For instance, virtually all of the claimed methods require synthesis of a stochastic population of polynucleotide sequences that are the screened or selected by virtue of a predetermined property. The only limitations added by claim 79 of the '476 patent are that the population has greater than 1 X 10^6 different sequences, and the sequences are synthesized by "stochastically copolymerizing" polynucleotides. In fact, claim 29 of the Kauffman '483 patent is broadly directed to a method of producing a stochastic polynucleotide population by any means, of any size. Thus, claim 79 of the '476 patent is a species of claim 29 of the '483 patent.

Moreover, the limitations of '476 claim 79 do not add a patentable distinction in view

of the state of the art at the time the Kauffman patent was filed. For instance, it would have been self-evident that the random generation of polynucleotides will naturally result in very large numbers of polynucleotides, because the number of permutations increases exponentially for each randomly incorporated unit. For example, a polynucleotide comprising only ten randomly incorporated bases has 4^{10} or over 10^6 random permutations. Thus, the size of the population recited in claim 79 is not a patentable distinction.

Furthermore, it was certainly known that new sequences could be made by ligating smaller polynucleotides together, i.e., *see* Lewin (1983), p. 285, and Shortle (1983), teaching that restriction fragments with cohesive, partly complementary "sticky" ends can be ligated together to form new DNA sequences. Thus, assuming that "stochastic copolymerization" has such a meaning, this would have been merely one known way to synthesize a population of stochastic sequences given the general teaching of and motivation for the method as taught by the invention as a whole. Thus, the manner of synthesizing stochastic sequences does not provide a patentable distinction.

Thus, '476 claim 79 would correspond to the count as obvious over the other claims, particularly claim 29 of the '483 patent, in view of the state of the art. Because claims 80-90 depend from claim 79, they define the same patentable invention and therefore would also correspond to the Count. In fact, claims 83 and 84 even specify that "stochastic copolymerization" is effected by hybridization of complementary sequences or by ligation, respectively, as already discussed above in reference to Maniatis (1982) and Shortle (1983).

Likewise, claim 103 corresponds exactly to part of the Count, but would also correspond in an obvious manner over claim 79. Claim 103 is directed to an isolated population of polynucleotides having greater than about 1 X 10^5 different sequences. If claim 79, a method of making a stochastic population of polynucleotide sequences, corresponds to the Count, then it follows that a population of stochastic polynucleotide sequences made thereby would also correspond. Thus, '476 claim 103 would also correspond to the Count because it is obvious over the other claims, as would claims 104-107 which depend from claim 103 and define the same patentable invention.

'476 claims 91-102

Finally, claim 91 of the '476 patent corresponds exactly to part of the Count. Even so, claim 91 would also be obvious over any one of a number of Kauffman claims in any of the five patents discussed herein, and would correspond to the Count in this manner as well. For instance, claim 91 recites a method of producing a diverse population of polynucleotides by stochastically copolymerizing polynucleotides which have been "cleaved," presumedly by a restriction endonuclease. Yet such a manner of producing nucleotide sequences was known in the art at the time as evidenced by Shortle (1983) and discussed above. Thus, claim 91 of the '476 patent does not provide a patentable distinction over any claim which recites a method of producing stochastic polynucleotide sequences, given the state of the art at the time. Since virtually all the method claims of the five Kauffman patents require a step whereby a

population of stochastic sequences is synthesized, a claim merely reciting a particular, but known, method of doing so would not patentably distinguish over the general method.

Thus, claim 91 of the '476 patent also corresponds to the Count in that it is obvious over the other claims. Because claims 92-102 depend from claim 91 and define the same patentable invention, claims 92-100 would also correspond to the Count in much the same manner as the other sets of dependent claims discussed at length above.

Thus, all the Kauffman '476 claims correspond to the proposed Count.

IV. CLAIMS OF THE HORWITZ APPLICATION WHICH CORRESPOND TO THE PROPOSED COUNT PURSUANT TO 37 CFR §1.607(A)(4)

Newly added claims 15-25 of the instant application are believed to correspond to the proposed Count. In addition, claims 3, 4, 6-8 and 11-14 submitted March 3, 1999, also correspond to the Count. The proposed Count includes all these claims joined by "or" to each other and to each of the Kauffman independent claims as discussed above. Each of the instant pending claims thus corresponds exactly to one part of the proposed Count. Because of the use of "or," correspondence to one part of the proposed Count is sufficient. Appendix B is a chart providing an element-by-element recitation of the newly added claims of the instant application

and exemplary support in both the originally filed and present application. [4]

V. EXPLANATION OF HOW THE REQUIREMENT OF 35 U.S.C. §135(b) IS MET

According to 35 U.S.C. §135(b), "[a] claim which is the same as, or for the same or substantially the same subject matter as, a claim of an issued patent may not be made in any application unless such a claim is made prior to one year from the date on which the patent was granted." In the instant case, the Kauffman '323 Patent issued on March 3, 1998. Claims 3, 4, 6-8 and 11-14 of the instant application were filed in a preliminary amendment in the instant application on March 3, 1999. These claims are for "the same as, or for the same or substantially the same subject matter as" claims 1, 16, 24, 25, 34 and 41 of the Kauffman '323 patent, and were present prior to one year from the date on which the Kauffman '323 Patent issued.

Likewise, the Kauffman '192 Patent issued on June 9, 1998. Claim 15 is submitted in the Supplemental Preliminary Amendment above, on this date, June 9, 1999. Claim 15 is for "the same as, or for the same or substantially the same subject matter as" the claim 1 of the Kauffman '192 patent, and is present prior to one year from the date on which this patent issued.

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[4]The present Horwitz application is the latest in a chain of continuation applications which begin with Serial No. 06/887,070, filed July 17, 1986. The present application is a continuation-in-part relative to the first application.

The Kauffman '483 patent issued on October 6, 1998. Claims 16-20 are submitted in the Supplemental Preliminary Amendment above, on this date, June 9, 1999. Claims 16-20 are for "the same as, or for the same or substantially the same subject matter as" claims 6, 17, 29, 35 and 36, respectively, of the Kauffman '483 patent, and are present prior to one year from the date on which this patent issued.

The Kauffman '514 patent issued on October 20, 1998. Claims 21-23 are submitted in the Supplemental Preliminary Amendment above, on this date, June 9, 1999. Claims 21-23 are for "the same as, or for the same or substantially the same subject matter as" claims 1, 12 and 18, respectively, of the Kauffman '514 patent, and are present prior to one year from the date on which this patent issued.

The Kauffman '479 patent issued on September 29, 1998. Claim 24 is submitted in the Supplemental Preliminary Amendment above, on this date, June 9, 1999. Claim 24 is directed to "the same as, or for the same or substantially the same subject matter as" claims 3 and 15, respectively, of the Kauffman '476 patent, and are present prior to one year from the date on which this patent issued.[5]

Not all independent Kauffman claims have been copied, since many are obvious variants of the claims which have been copied, as discussed above in Section III, "Identification of claims of the Kauffman patents which correspond to the proposed Count pursuant to 37 CFR §1.607(a)(3)." However, all independent Kauffman claims have been included in the alternative in the proposed Count to avoid any question of having satisfied the requirements of 37 CFR §1.606, which requires that the Count not be narrower than any patent claim that is designated as corresponding to the Count.

VI. EXPLANATION OF WHY AN INTERFERENCE SHOULD BE DECLARED

As stated in 37 C.F.R. §1.601(i), "[a]n *interference* is a proceeding instituted in the Patent and Trademark Office before the Board to determine any question of patentability and priority of invention between two or more parties claiming the same patentable invention" [emphasis in original]. According to 37 C.F.R. §1.601(n), "[i]nvention A is the *same patentable invention* as an invention 'B' when invention 'A' is the same as (35 U.S.C. §102) or is obvious (35 U.S.C. §103) in view of invention 'B' assuming invention 'B' is prior art with respect to invention 'A'" [emphasis in original].

Claims 1-48 of the Kauffman '323 Patent define the same patentable invention as claims 1-5 of the Kauffman '192 Patent and as claims 1-53 of the Kauffman '483 Patent and as claims 1-46 of the Kauffman '514 Patent and as claims 1-107 of the Kauffman '476 Patent and as claims 3, 4, 6-8 and 11-25 of the instant Horwitz application. All the claims are essentially directed to or based on methods of searching for biologically active nucleotide sequences from among a randomly or stochastically generated population, on the theory that particular novel sequences capable of predetermined or desired biological functions may be identified. The crux of the invention reflected in all the claims rests on the discovery, which was indeed a "leap of faith" at the time the present invention was made, that randomly generated sequences could perform specific biological functions in the absence of millions of years of evolutionary refinement. While many of the claims in the various Kauffman patents and the corresponding claims submitted in the present application incorporate additional steps beyond the generation

and screening of or selecting for randomly generated sequences having a particular function, such steps do not make a patentable difference when considering the state of the art at the time.

Indeed, it was known at the time that polynucleotides could be cloned into expression vectors, and that such vectors could be transformed into and amplified in an appropriate host cell. It was known that such a host cell could be analyzed, tested or selected based on whether it expressed the protein encoded by or displayed the function provided by the cloned nucleotide sequence. It was known that vector could then be isolated from identified transformed cells and the cloned nucleotide sequence could then be isolated from the vector using standard techniques in the art, i.e., restriction and gel purification. And it was known that such host cells could be used to produce the recombinant protein, which could be purified and used for whatever purpose it was sought, i.e., for vaccine development, as a drug, to raise antibodies, etc. Such manipulations of nucleic acids and standard recombinant techniques do not impart a patentable distinction to the novel premise at the time that a completely random population of nucleotides could generate a sequence having a particular biological activity.

Likewise, while many of the claims in the various Kauffman patents and the corresponding claims submitted in the present application incorporate limitations which more precisely define the manner in which nucleotide sequences are generated, or the manner in which nucleotide sequences are screened, or the particular predetermined or desired property of the nucleotide sequence identified, these specific limitations are merely variations of the general concept, and apparent applications of the method, given the state of the art at the time.

Indeed, it was known that nucleotide sequences could be synthesized chemically or by using enzymes like polymerase and terminal transferase. It was known that new nucleotide sequences could be generated by ligating smaller nucleotide sequences together. It was known that DNA could be cleaved with restriction enzymes and re-ligated using DNA ligase following hybridization of the "sticky ends" of the cleaved DNA. And it was also known that DNA could be ligated in the absence of complementary ends, i.e., blunt-end ligation.

Thus, while there are many claims which have issued in the five Kauffman patents, each merely rephrases the crux of the invention, or adds or specifies particular steps, which would have been apparent to a person skilled in the art when the basic novelty of the invention is taken in view of the state of the art. Furthermore, while the language of the Kauffman claims is slightly different than the instant claims, i.e. "stochastic" instead of "random, without regard to a wild type sequence" each set of claims is based on the same novel premise: that novel nucleotide sequences may be identified in a random population which have or exhibit a desired biological activity.[6]

Therefore, because the Kauffman and Horwitz claims define the same patentable invention, an interference between claims 1-48 of the Kauffman '323 Patent, claims 1-5 of the

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[6] "Random, without regard to a wild type sequence," emphasizes the manner in which the present invention distinguishes over the prior art. Oligonucleotides for the typical mutagenesis experiment of the prior art were synthesized with a bias toward wild type. In contrast, the present invention requires no prior knowledge of structure-function relationships. However, this language does not preclude situations where there is knowledge of a wild type sequence. Rather, it merely indicates that such knowledge is not required.

Kauffman '192 Patent, claims 1-53 of the Kauffman '483 Patent, claims 1-46 of the Kauffman '514 Patent, claims 1-107 of the Kauffman '476 Patent and claims 3, 4, 6-8 and 11-25 of the instant Horwitz application should be declared.

With regard to the Kauffman applications which are thought to be still pending at the Patent & Trademark Office, while applicants do not have specific knowledge of any claim in such applications, given the fact that all the claims in the five issued Kauffman patents are directed to the same patentable invention as disclosed and claimed in the present application, applicants suspect that any pending Kauffman application should also be included in the interference. Indeed, in view of the many ways in which Kauffman has defined the same invention through the claims of the five issued patents, it is expected that Kauffman will repackage the invention in as many ways as are linguistically possible in any applications which remain pending.

The Examiner is respectfully requested to review any related pending application as to whether such application contains claims which are directed to the same patentable invention as defined by those discussed herein, and determine whether such application or applications should be included in the interference. If necessary, the Examiner is respectfully requested to suggest a claim to applicants corresponding to the claims in any pending application pursuant to 37 CFR 1.605(a) so that all related applications may be included in the interference.

VII. CONCLUSION

Applicants respectfully request than an interference be declared employing the proposed Count set forth on attached Appendix A between claims 1-48 of the Kauffman '323 Patent, claims 1-5 of the Kauffman '192 Patent, claims 1-53 of the Kauffman '483 Patent, claims 1-46 of the Kauffman '514 Patent, claims 1-107 of the Kauffman '476 Patent and claims 3, 4, 6-8 and 11-25 of the instant Horwitz application, all designated as corresponding to the Count. In addition, Applicants respectfully request that any pending Kauffman applications containing claims directed to the same patentable invention as defined in the Count be included in the interference as well. Such action is respectfully requested.

Respectfully submitted,

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APPENDIX A
PROPOSED COUNT

A method of identifying a peptide, polypeptide or protein having a binding property to a ligand, comprising:

(a) providing a ligand for detecting said binding property;

(b) synthesizing a diverse population of stochastically generated polynucleotide sequences;

(c) inserting said diverse population of stochastically generated polynucleotide sequences into a population of expression vectors to form a diverse population of expression vectors containing stochastically generated polynucleotide sequences;

(d) expressing in host cells said diverse population of expression vectors containing stochastically generated polynucleotide sequences to produce a diverse population of peptides, polypeptides or proteins; and

(e) screening said diverse population of peptides, polypeptides or proteins with said ligand under conditions which allow binding and detection of one or more peptides, polypeptides or proteins having said predetermined property.

or

An isolated, diverse population of peptides, polypeptides, or proteins comprising greater than about 1×10^5 different stochastic amino acid sequences encoded by stochastic polynucleotide sequences.

or

A method of isolating a polynucleotide sequence encoding a peptide, polypeptide or protein having a predetermined binding property to a ligand, comprising:

(a) providing a ligand for detecting said binding property;

(b) synthesizing a diverse population of stochastically generated polynucleotide sequences;

(c) inserting said diverse population of stochastically generated polynucleotide sequences into a population of expression vectors to form a diverse population of expression vectors containing stochastically generated polynucleotide sequences;

(d) expressing in host cells said diverse population of expression vectors containing stochastically generated polynucleotide sequences to produce a diverse population of peptides, polypeptides or proteins;

(e) screening said diverse population of peptides, polypeptides or proteins with said ligand under conditions which allow binding and detection of one or more peptides, polypeptides or proteins to said ligand; and

(f) isolating the stochastically generated polynucleotide sequence or sequences which encoding said peptides, polypeptides or proteins having said predetermined binding property to said ligand.

or

An isolated, diverse population of polynucleotide sequences which encode a diverse population of ligand binding peptides, polypeptides, or proteins comprising greater than about $1x10^5$ different stochastic amino acid sequences encoded by the stochastic polynucleotide sequences.

or

A method of isolating a peptide, polypeptide or protein having a binding property, comprising:

(a) providing a ligand for detecting said binding property;

(b) synthesizing a diverse population of stochastically generated polynucleotide sequences;

(c) inserting said diverse population of stochastically generated polynucleotide sequences into a population of expression vectors to form a diverse population of expression vectors containing stochastically generated polynucleotide sequences;

(d) expressing in host cells said diverse population of expression vectors containing stochastically generated polynucleotide sequences to produce a diverse population of peptides, polypeptides or proteins;

(e) screening said diverse population of peptides, polypeptides or proteins with said ligand under conditions which allow binding and detection of one or more peptides, polypeptides or proteins having said predetermined property;

(f) isolating the stochastically generated polynucleotide sequence or sequences encoding said peptides, polypeptides or proteins having said binding property to said ligand; and

(g) using genetic information from said isolated stochastically generated polynucleotide sequence to produce said peptide, polypeptide or protein having said binding property.

or

A method of producing a diverse population of stochastically generated polynucleotide sequences encoding a diverse population of ligand binding peptides, polypeptides or proteins, comprising:

(a) synthesizing a diverse population of stochastically generated polynucleotide sequences selected from a method consisting of stochastic copolymerization of double stranded oligonucleotides, copolymerization of the four kinds of nucleotide triphoshpates consisting of Adenine, Cytosine, Guanine and Thymine, and chemical synthesis; and

(b) inserting said diverse population of stochastically generated polynucleotide sequences into a population of vectors to form a diverse population of vectors containing stochastically generated polynucleotide sequences.

or

An isolated, diverse population of vectors comprising stochastically generated polynucleotide sequences encoding a diverse population of ligand binding peptides, polypeptides, or proteins comprising greater than about $1x10^5$ different stochastic amino acid sequences.

or

An isolated, diverse population of peptides or polypeptides comprising stochastic amino acid sequences encoded by stochastic polynucleotide sequences of about 300 nucleotides or less in length.

or

An isolated, diverse population of polynucleotides sequences encoding a diverse population of ligand binding peptides or polypeptides comprising stochastic amino acid sequences encoded by stochastic polynucleotide sequences of about 300 nucleotides or less in length.

or

An isolated, diverse population of vectors encoding a diverse population of ligand binding peptides or polypeptides comprising stochastic amino acid sequences encoded by stochastically generated polynucleotide sequences of about 300 nucleotides or less in length.

or

An isolated, diverse population of peptides, polypeptides, or proteins comprising stochastic amino acid sequences produced by a method comprising synthesizing a diverse population of stochastically generated polynucleotide sequences selected from a method

consisting of stochastic copolymerization of double stranded oligonucleotides, copolymerization of the four kinds of nucleotide triphosphates consisting of Adenine, Cytosine, Guanine and Thymine, and chemical synthesis; and expressing said stochastically generated polynucleotide sequences.

or

A process for the production of a peptide, polypeptide, or protein having a predetermined property, comprising the steps of:

producing by enzymatic or chemical coupling, stochastically generated polynucleotide sequences;

forming a library of expression vectors containing such stochastically generated polynucleotide sequences;

culturing host cells containing the vectors to produce peptides, polypeptides, or proteins encoded by the stochastically generated polynucleotide sequences;

carrying out screening or selection on such host cells, to identify a peptide, polypeptide, or protein produced by the host cells having the predetermined property;

isolating a stochastically generated polynucleotide sequence which encodes the identified peptide, polypeptide, or protein;

using the isolated sequence to produce the peptide, polypeptide, or protein having the predetermined property.

or

A process for the production of a peptide, polypeptide, or protein having a predetermined property, comprising the steps of:

producing by synthetic polynucleotide coupling, a population of stochastically generated polynucleotide sequences;

forming a library of expression vectors containing said population of stochastically generated polynucleotide sequences;

introducing the vectors into host cells;

culturing the host cells;

carrying out screening or selection on said host cells, to identify a peptide, polypeptide, or protein produced by the host cells having the predetermined property;

isolating a stochastically generated polynucleotide sequence which encodes the identified peptide, polypeptide, or protein;

using the isolated sequence to produce the peptide, polypeptide, or protein having the predetermined property.

or

A process for the production of a peptide, polypeptide, or protein having a predetermined property, comprising the steps of:

producing a population of at least partially stochastic synthetic polynucleotide sequences;

introducing the population of at least partially stochastic polynucleotide sequences into host cells to produce transformed host cells;

cultivating the transformed host cells to produce peptides, polypeptides, or proteins expressed by at least some of the stochastic polynucleotide sequences;

carrying out screening and/or selection methods on said transformed host cells to identify clones producing the peptide, polypeptide, or protein having the predetermined property;

isolating the clones so identified; and

growing the isolated clones in a manner so as to produce the peptide, polypeptide, or protein having the predetermined property.

or

A process for the detection or titration of a ligand using a peptide, polypeptide, or protein having a predetermined property, comprising the steps of:

producing by synthetic polynucleotide coupling, a population of stochastically generated polynucleotide sequences;

forming a library of expression vectors containing said population of stochastically generated polynucleotide sequences;

introducing the vectors into host cells;

culturing the host cells containing the vectors to produce peptides, polypeptides, or proteins encoded by the stochastically generated polynucleotide sequences;

carrying out screening or selection on said host cells, to identify a peptide, polypeptide, or protein produced by the host cells having the predetermined property;

contacting the peptide, polypeptide, or protein with two or more concentrations of a ligand; and

determining the amount of peptide, polypeptide or protein bound at each concentration of ligand.

or

A process for the detection or titration of a ligand using a peptide, polypeptide, or protein having a predetermined property, comprising the steps of:

producing a population of at least partially stochastic synthetic polynucleotide sequences;

introducing the population of at least partially stochastic polynucleotide sequences into host cells to produce transformed host cells;

cultivating the transformed host cells to produce peptides, polypeptides, or proteins expressed by at least some of the stochastic polynucleotide sequences;

carrying out screening and/or selection methods on said transformed host cells to identify clones producing the peptide, polypeptide, or protein having the predetermined property;

contacting the peptide, polypeptide, or protein with two or more concentrations of a ligand; and

determining the amount of peptide, polypeptide or protein bound at each concentration of ligand.

or

A method of identifying a peptide, polypeptide or protein having a predetermined property, comprising:

(a) producing a population of peptides, polypeptides or proteins encoded by stochastic polynucleotide sequences;

(b) screening said population of peptides, polypeptides or proteins for said predetermined property under conditions which allow detection of one or more peptides, polypeptides or proteins having said predetermined property.

or

A method of producing a peptide, polypeptide or protein having a predetermined property, comprising:

(a) producing a population of peptides, polypeptides or proteins encoded by stochastic polynucleotide sequences;

(b) screening said population of peptides, polypeptides or proteins for said predetermined property under conditions which allow detection of one or more peptides, polypeptides or proteins having said predetermined property;

(c) isolating the polynucleotide sequence encoding said one or more peptides, polypeptides or proteins having said predetermined property; and

(d) producing said peptide polypeptide or protein.

or

A method of producing a stochastic polynucleotide population, comprising synthesizing stochastic polynucleotide sequences.

or

A method of producing a desired compound, comprising combining a population of peptides, polypeptides or proteins encoded by stochastic polynucleotide sequences with two or more reactant precursors under conditions favorable for said precursors to react, and incubating said population of peptides, polypeptides or proteins with said reactant precursors for sufficient time so as to allow the catalysis of said desired compound.

or

A method of identifying a population of peptides, polypeptides or proteins which catalyze a sequence of chemical reactions, comprising:

(a) combining a population of peptides, polypeptides or proteins encoded by stochastic polynucleotide sequences with two or more reactant precursors under conditions favorable for said precursors to react;

(b) incubating said population of peptides, polypeptides or proteins with said reactant precursors for sufficient time to allow the catalysis of said sequence of chemical reactions, and

(c) determining the presence or absence of a compound produced by said sequence of chemical reactions, the presence of said compound indicating that said population of peptides, polypeptides or proteins can catalyze said sequence of chemical reactions.

or

A process for the production of an expression vector which comprises at least one stochastic sequence of polynucleotides, comprising the steps of:

providing in an appropriate buffer at least three different sequences of oligonucleotides, said oligonucleotides each comprising at least 7 nucleotide residues;

polymerizing said oligonucleotides to form a stochastic sequence of polynucleotides; and ligating said stochastic sequence of polynucleotides into a linearized expression vector.

or

A process for the production of an expression vector capable of producing a transcription product or a translation product comprising at least one stochastic sequence of polynucleotides, comprising the steps of:

linearizing an expression vector;

reacting said linearized expression vector with terminal transferase enzyme in the presence of desired ratios of deoxynucleotide-triphosphates of guanine, cytosine, thymidine, and adenine to form a stochastic polynucleotide sequence at each 3' extremity of said linearized vector;

hybridizing said stochastic polynucleotide sequence at a 3' extremity of said linearized vector; and

synthesizing a second strand from said 3' ends of said hybridized vector by incubating with polymerase.

or

A process for the production of a library of expression vectors capable of producing a transcription product or a translation product, said vectors comprising at least one stochastic sequence of polynucleotides, comprising the steps of:

producing at least one stochastic sequence of polynucleotides;

ligating said stochastic sequence of polynucleotides into an expression vector;

transforming a competent clone with said ligated expression vector;

culturing said transformed clone;

screening and/or selecting said transformed clone in order to isolate a clone expressing a stochastic polynucleotide leading to the synthesis of a transcription product or a translation product;

isolating said selected or screened transformed clone; and

isolating the expression vector cultured in said selected or screened transformed clone so identified.

or

A method of producing a diverse population of vectors comprising:

(a) synthesizing a diverse population of stochastically generated polynucleotide sequences comprising greater than about 1 x 10^5 different polynucleotide sequences, said method consisting of stochastic copolymerization of double stranded oligonucleotides, copolymerization of the four kinds of nucleotide triphosphates consisting of adenine, cytosine, guaninie and thymine, and chemical synthesis, and

(b) inserting said diverse population of stochastically generated polynucleotide sequences into a population of vectors to form a diverse population of vectors containing stochastically generated polynucleotide sequences.

or

A method of producing a diverse population of vectors, comprising stochastically copolymerizing a diverse population of vectors containing double stranded polynucleotides so as to produce a new population of vectors containing greater than about 1 x 10^5 different polynucleotide sequences.

or

A method of producing a diverse populations of vectors, comprising:

(a) obtaining one or more diverse populations of vectors containing diverse sequences of double stranded polynucleotides;

(b) digesting the one or more diverse populations of vectors with a restriction enzyme, and

(c) stochastically copolymerizing the one or more diverse populations of double stranded polynucleotides so as to produce a new population of greater than about 1×10^5 different polynucleotide sequences.

or

A process for the production of a transcription product or a translation product, comprising the steps of:

producing a stochastically-generated polynucleotide sequence;

producing a library of expression vectors comprising said stochastic polynucleotide sequence;

transforming or transfecting a competent clone with said library of expression vectors:

amplifying said transformed or transfected competent clone;

screening and/or selecting said transformed or transfected clone in order to isolate a clone expressing a stochastic polynucleotide sequence capable of synthesizing a transcription product or a translation product having a predetermined property; and

isolating said selected or screened transformed clone;

isolating a stochastically generated polynucleotide sequence which encodes the identified transcription product or translation product using the isolated sequence to produce the transcription product or translation product having the predetermined property.

or

A process for the production of a transcription product or a translation product, comprising the steps of:

producing a diverse population of stochastic polynucleotide sequences;

inserting said stochastic polynucleotide sequences into expression vectors to form a diverse population of expression vectors;

transforming or transfecting competent clones with said diverse population of expression vectors comprising said stochastic polynucleotide sequences;

amplifying said transformed or transfected competent clone;

screening and/or selecting said transformed or transfected clones in order to isolate a clone expressing a stochastic polynucleotide capable of synthesizing a transcription product or a translation product having the predetermined property;

isolating said selected or screened transformed clone;

isolating said stochastic polynucleotide sequence which encodes the identified transcription product or translation product;

using the isolated stochastic polynucleotide sequence so as to produce the transcription product or translation product having the predetermined property.

or

A process for the production of a polynucleotide comprising,

producing in an appropriate buffer a diverse population of stochastic polynucleotide sequences;

inserting said stochastic polynucleotide sequences into vectors to form a diverse population of vectors;

introducing said diverse population of vectors into host cells in a manner to produce a diverse population of transformed host cells;

producing independent clones of the host cells so produced;

screening and/or selecting said independent clones of the host cells to identify host cells comprising a stochastic polynucleotide sequence having at least one desired property; and

isolating said stochastic polynucleotide sequence from the selected or screened clones of host cells.

or

A process for the production of an RNA comprising, producing in an appropriate buffer a diverse population of stochastic polynucleotide sequences;

inserting said stochastic polynucleotide sequences into vectors to form a diverse population of vectors;

introducing said diverse population of vectors into host cells in a manner to produce a diverse population of transformed host cells;

producing independent clones of transformed or transfected host cells;

screening and/or selecting said independent clones of the host cells to identify host cells comprising a stochastic polynucleotide sequence capable of producing RNA having at least one desired property; and

isolating said stochastic polynucleotide sequence from the selected or screened clones of host cells.

or

A method of identifying a polynucleotide having a predetermined property, comprising:

(a) producing a population of polynucleotides comprising greater than about 1×10^5 different stochastic polynucleotide sequences;

(b) screening said population of polynucleotides for said predetermined property under conditions which allow detection of one or more polynucleotides having said predetermined property.

or

A method of identifying a polynucleotide having a binding property to a ligand, comprising:

(a) synthesizing a population of stochastic polynucleotide sequences;

(b) inserting said population of stochastic polynucleotide sequences into a population of vectors to form a population of vectors containing stochastic polynucleotide sequences;

(c) expressing in host cells said population of vectors containing stochastic polynucleotide sequences to produce a diverse population of expressed polynucleotides, and

(d) screening said diverse population of polynucleotides with a ligand under conditions which allow binding and detection one or more polynucleotides having said binding property to said ligand.

or

A method of isolating a polynucleotide having a predetermined property, comprising:

(a) producing a population of polynucleotides comprising greater than 1×10^5 different stochastic polynucleotide sequences;

(b) screening said population of stochastic polynucleotide sequences for said predetermined property under conditions which allow detection of one or more polynucleotides having said predetermined property, and

(c) isolating the one or more polynucleotide sequences having said predetermined property.

or

A method of isolating a polynucleotide having a binding property to a ligand, comprising:

(a) synthesizing a population of stochastic polynucleotide sequences;

(b) inserting said population of stochastic polynucleotide sequences into a population of vectors to form a population of vectors containing stochastic polynucleotide sequences;

(c) expressing in host cells said population of vectors containing stochastic polynucleotide sequences to produce a diverse population of expressed polynucleotides, and

(d) screening said diverse population of polynucleotides with a ligand under conditions which allow binding and detection of one or more polynucleotides to said ligand, and

(e) isolating the stochastic polynucleotide sequence or sequences having said binding property to said ligand.

or

A method of producing a diverse population of polynucleotides, comprising stochastically copolymerizing a population of polynucleotides so as to produce a new population of polynucleotides containing greater than about 1.times.10.sup.6 different polynucleotide sequences.

or

A method of producing a diverse population of polynucleotides, comprising:

(a) obtaining one or more populations of polynucleotides;

(b) cleaving the one or more populations of polynucleotides, and

(c) stochastically copolymerizing the one or more populations of cleaved polynucleotides so as to produce a new population of greater than about 1 x 10 different polynucleotide sequences.

or

An isolated population of polynucleotides, comprising greater than about 1×10^5 different stochastic polynucleotide sequences.

APPENDIX B

APPLICATION OF HORWITZ CLAIMS TO THE DISCLOSURE OF THE HORWITZ APPLICATIONS[7,8]

3. A method of identifying a functional nucleotide sequence which provides a desired biological activity comprising:	Page 2, lines 9-10 (page 3, lines 19-20)
a. providing a means for detecting said desired biological activity;	Page 5, lines 22-24 (page 5, lines 20-21)
b. synthesizing a mixed population of random nucleotide sequences by enzymatic or chemical synthesis without regard to a wild type sequence;	The phrase "random, without regard to a wild type sequence" means that the random population retains no bias to wild type as was seen in a typical mutagenesis experiment at the time the invention was made. For instance, as discussed at page 8, lines 14-19, the process "extends beyond the use of mutagenesis merely as a tool to study the nature of *regions* of DNA encoding specific biological activity." Likewise, at page 28, lines 1-4, "prior knowledge of structure-function relationships with respect to specific regions of DNA is not required." (Page 1, lines 21-23) Support for "enzymatic or chemical synthesis" is found on page 25, lines 30-32. (page 24, lines 28-30)
c. introducing a plurality of said random nucleotide sequences into a population of	Page 4, line 14; page 5, lines 1-3 (page 4, lines 7-8)

The support provided for the Horwitz claims corresponding to the proposed Count is merely exemplary and is not meant to imply that additional support cannot be found in the Horwitz specification and claims as originally filed. Corresponding exemplary support in parent application Serial No. 06/887,070, filed July 17, 1986, is set forth in parentheses.

For steps, phrases or words in claims which are used more than once, exemplary support may be shown by referring to a previous claim by the phrase "see above."

cloning vectors to obtain a plurality of cloning vectors containing random nucleotide sequences;	
d. introducing said cloning vectors into suitable host cells;	Page 4, lines 12-14 (page 3, lines 18-19)
e. expressing said cloning vectors in said host cells; and	Page 5, lines 3-8 (page 4, lines 34-38)
f. screening said host cells using said means for detecting the desired biological activity under conditions which allow detection of one or more host cells comprising vectors which comprise a functional nucleotide sequence which provides the desired biological activity.	Page 7, lines 26-29 (page 7, lines 34-37)
4. A method of isolating a functional nucleotide sequence which provides a desired biological activity comprising:	Page 2, lines 16-22 Page 30, lines 30-31 (page 5, lines 14-16; page 8, lines 27-31)
b. synthesizing a mixed population of random nucleotide sequences by enzymatic or chemical synthesis without regard to a wild type sequence; c. introducing a plurality of said random nucleotide sequences into a population of cloning vectors to obtain a plurality of cloning vectors containing random nucleotide sequences; d. introducing said cloning vectors into suitable host cells; e. expressing said cloning vectors in said host cells; f. screening said host cells using said means for detecting the desired biological activity under conditions which allow detection of one or more host cells comprising vectors which comprise a functional nucleotide sequence which	See above for claim 3.

provides the desired biological activity; and	
g. isolating said nucleotide sequence or sequences which provide the desired biological activity.	See above for preamble.
6. A method of isolating a host cell which comprises a functional nucleotide sequence which produces a desired biological activity comprising:	Page 5, lines 28-29 (page 5, lines 11-13) Paragraph bridging pages 6-7 (page 7, lines 20-28)
a. providing a means for detecting said desired biological activity; b. synthesizing a mixed population of random oligonucleotides by enzymatic or chemical synthesis without regard to a wild type sequence; c. introducing a plurality of random oligonucleotides into a population of cloning vectors to obtain a plurality of cloning vectors containing random oligonucleotides; d. introducing said cloning vectors into suitable host cells; e. expressing said cloning vectors in said host cells; f. screening said host cells to determine whether the inserted oligonucleotide provides the desired biological activity;	See above for claim 3.
g. isolating said host cells having said oligonucleotide having the desired biological activity.	See above for preamble.
7. A method of producing a mixed population of random nucleotide sequences in order to identify one or more functional sequences which provide a desired biological activity comprising:	See above for claim 3.

a. synthesizing a mixed population of random nucleotide sequences in a manner by which the frequency of stop codons in said mixed population is reduced; and	Page 24, lines 24-29 (page 25, lines 20-24)
b. inserting said mixed population of random nucleotide sequences into a population of cloning vectors to form a mixed population of vectors containing randomly generated sequences.	See above for claim 3, step c.
8. An isolated, mixed population of vectors comprising randomly generated nucleotide sequences encoding a mixed population of amino acid sequences and having a reduced frequency of stop codons as compared to codons encoding amino acids.	Page 5, lines 9-10 Page 30, lines 30-31 (page 5, lines 6-7) See above for claim 7.
11. An isolated, mixed population of random nucleotide sequences comprising a nucleotide sequence providing a desired biological activity produced by a method comprising synthesizing a mixed population of random nucleotide sequences in a manner which results in stop codon bias, and introducing a plurality of said randomly generated nucleotide sequences into a population of cloning vectors to form a mixed population of vectors containing randomly generated nucleotide sequences.	See above for claims 3, 7 and 8.
12. A method of identifying a functional nucleotide sequence which provides a desired biological activity comprising: a. providing a means for detecting said desired biological activity;	See above for claim 3.

b. synthesizing a mixed population of random nucleotide sequences in a manner by which the frequency of stop codons in said mixed population is reduced;

See above for claim 7.

c. introducing a plurality of random nucleotide sequences into a population of cloning vectors to obtain a plurality of cloning vectors containing random nucleotide sequences;

d. introducing said cloning vectors into suitable host cells;

e. expressing said cloning vectors in said host cells; and

f. screening said host cells using said means for detecting the desired biological activity under conditions which allow detection of one or more host cells comprising vectors which comprise a functional nucleotide sequence which provides the desired biological activity.

13. A method of identifying a peptide, polypeptide or protein having a desired biological activity comprising:

Page 7, lines 21-24
(page 7, lines 29-32)

Also, see above for claim 3.

a. providing a means for detecting said desired biological activity;

b. synthesizing a mixed population of random nucleotide sequences by enzymatic or chemical synthesis without regard to a wild type sequence;

c. introducing a plurality of said random nucleotide sequences into a population of cloning vectors to obtain a plurality of cloning vectors containing random nucleotide sequences;

d. introducing said cloning vectors into suitable host cells;

e. expressing said cloning vectors in said host cells to produce a random population of peptides, polypeptides or proteins; and

f. screening said random population of peptides, polypeptides or proteins with said means for detecting the desired biological activity under conditions which allow detection of one or more peptides, polypeptides or proteins from said random population having the desired biological activity.

14. A method of identifying a peptide, polypeptide or protein capable of reacting with a substrate:	Page 7, lines 26-29 (page 7, lines 35-37)
a. providing a substrate;	
b. synthesizing a mixed population of random nucleotide sequences by enzymatic or chemical synthesis without regard to a wild type sequence;	See above for claim 3.
c. introducing a plurality of said random nucleotide sequences into a population of cloning vectors to obtain a plurality of cloning vectors containing random nucleotide sequences;	
d. introducing said cloning vectors into suitable host cells;	
e. expressing said cloning vectors in said host cells to produce a random population of peptides, polypeptides or proteins; and	
f. screening said random population of peptides, polypeptides or proteins with said substrate under conditions which allow detection of one or more peptides, polypeptides or proteins from said random population which react with said substrate.	See above for preamble.
15. A process for the production of a peptide or protein having a desired biological activity comprising the steps of: producing by enzymatic or chemical	Page 5, lines 1-3, 20-22 Page 7, lines 21-24 (paragraph bridging pages 6 and 7)

synthesis a random population of nucleotide sequences without regard to a wild type sequence;	See above for claim 3.
forming a library of expression vectors containing the random population of nucleotide sequences;	
culturing host cells containing the vectors to produce peptides or proteins encoded by the random population of nucleotide sequences;	
carrying out screening or selection on the host cells, to identify a peptide or protein produced by the host cells having the desired biological function;	Page 2, lines 32-35 Page 6, lines 35-37 (page 7, lines 34-37) (page 7, lines 20-24)
isolating a randomly synthesized nucleotide sequence which encodes the identified peptide or protein;	See above for claim 4.
using the isolated sequence to produce the peptide or protein having the desired biological activity.	Page 7, lines 24-26 (page 6, line 36)
16. A method of identifying a peptide or protein having a desired biological activity, comprising: (a) producing a population of peptides or proteins encoded by random nucleotide sequences produced by enzymatic or chemical synthesis without regard for a wild type sequence; and (b) screening said population of peptides or proteins for said desired biological activity under conditions which allow detection of one or more peptides or proteins having said desired biological activity.	See above for claim 15.
17. A method of producing a peptide or	Page 7, lines 21-26

protein having a desired biological function, comprising:

(page 6, line 36)

(a) producing a population of peptides or proteins encoded by random nucleotide sequences produced by enzymatic or chemical synthesis without regard for a wild type sequence;

See above for claim 3.

(b) screening said population of peptides or proteins for said desired biological function under conditions which allow detection of one or more peptides, polypeptides or proteins having said desired biological function;

(c) isolating the nucleotide sequence(s) encoding said one or more peptides or proteins having said desired biological property; and

See above for claim 4.

(d) producing said peptide or protein.

See above for preamble.

18. A method of producing a random polynucleotide population for use in screening for a desired biological function, comprising adding random nucleotides to an expression vector without regard to a wild type sequence.

Page 5, lines 20-22
(page 5, lines 18-20)

Page 25, lines 30-37
(page 24, lines 28-35)

Also, see above for claim 3.

19. A method of generating a product of an enzyme-substrate reaction, comprising combining a population of peptides or proteins encoded by random nucleotide sequences produced without regard to a wild type sequence with substrate under conditions such that said enzyme-substrate reaction may occur, and incubating said population of peptides or proteins with said substrate such that said product may be

Page 7, lines 24-29
(page 7, lines 32-37)

Also, see above for claim 3.

detected.

20. A method of identifying a population of peptides or proteins which catalyze an enzyme substrate reaction, comprising: (a) combining a population of peptides or proteins encoded by random nucleotide sequences produced without regard to a wild type sequence with substrate under conditions such that said enzyme-substrate reaction may occur; (b) incubating said population of peptides or proteins with said enzyme substrate so that a product of said enzyme-substrate reaction may be generated; and (c) screening for the product of the enzyme-substrate reaction to identify a population of peptides or proteins which catalyze said enzyme-substrate reaction.	See above for claim 19.
21. A process for the production of an expression vector capable of transcribing or translating an open reading frame to produce a desired biological function, said vector comprising a random nucleotide sequence, comprising the steps of:	Page 5, lines 1-8 Page 6, lines 29-33 (paragraph bridging pages 4 and 5)
producing a random population of nucleotide sequences by enzymatic or chemical synthesis without regard to a wild type sequence; ligating said random population of nucleotide sequences into an expression vector to form a library of expression vectors; transforming suitable host cells with said library of expression vectors; growing the transformed host cells containing said expression vectors;	See above for claim 3.

screening said transformed host cells in order to identify an expression vector capable of transcribing or translating an open reading frame to produce the desired biological function, or selecting said host cells containing an expression vector capable of transcribing or translating an open reading frame to produce the desired biological function;	See above for preamble.
isolating the identified or selected transformed host cell; and	See above for claim 6.
isolating the expression vector from said isolated host cell line.	Page 30, lines 30-31 (page 8, lines 30-31)
22. A method for producing a random population of vectors comprising:	See above for claim 3, step c.
(a) synthesizing a heterogenous population of truly random nucleotide sequences comprising about a billion different nucleotide sequences, said method consisting of random ligation of oligonucleotides or random addition of nucleotide triphosphates without regard to a wild type sequence, and	Page 9, lines 4 (page 15, line 20) Page 4, lines 30-36 (page 3, lines 34-36; page 4, lines 25-31) Page 25, lines 30-32 (page 24, lines 33-35)
(b) inserting said heterogenous population of random nucleotide sequences into a population of vectors to form a heterogenous population of vectors containing random nucleotide sequences.	See above for preamble.
23. A process for the production of a nucleotide sequence comprising,	See above for claims 3, 4 and 15.
producing a heterogenous population of random nucleotide sequences by enzymatic or chemical synthesis without regard to a wild type sequence;	Page 16, line 32; page 17, line 6 (page 20, lines 17-21)
inserting said population of random nucleotide sequences into vectors to form a	

random population of vectors;

introducing said random population of vectors into host cells in a manner to produce a random population of transformed host cells;

growing independent colonies from the transformed host cells;

screening and/or selecting said colonies of the host cells to identify host cells comprising a nucleotide sequence having a desired biological activity; and

isolating said nucleotide sequence from the selected or screened host cells.

24. A method of identifying a nucleotide sequence having a desired biological activity, comprising: (a) producing a population of nucleotide sequences comprising greater about a billion different random nucleotide sequences by enzymatic or chemical synthesis without regard to a wild type sequence; (b) screening said population of nucleotide sequences for said desired biological activity under conditions which allow detection of nucleotide sequences having said desired biological activity.	See above for claims 3 and 22.
25. A method of identifying a functional nucleotide sequence which provides a desired biological activity comprising: a. providing a means for detecting said desired biological activity; b. forming a population of cloning vectors, each containing a random nucleotide sequence produced by enzymatic or chemical synthesis without regard to a wild type sequence;	See above for claim 3.

c. introducing said cloning vectors into suitable host cells;

d. expressing said cloning vectors in said host cells; and

e. screening said host cells using said means for detecting the desired biological activity under conditions which allow detection of one or more host cells comprising vectors which comprise a functional nucleotide sequence which provides the desired biological activity.